

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07B 59/00, C08F 30/04, C07C 277/08, 279/06 // C07M 5:00	A1	(11) International Publication Number: WO 99/18053 (43) International Publication Date: 15 April 1999 (15.04.99)
(21) International Application Number: PCT/CA98/00933 (22) International Filing Date: 2 October 1998 (02.10.98) (30) Priority Data: 60/060,886 2 October 1997 (02.10.97) US (71) Applicant (for all designated States except US): THE UNIVERSITY OF WESTERN ONTARIO [CA/CA]; Stevenson-Lawson Building, London, Ontario N6A 5B8 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): HUNTER, Duncan, H. [CA/CA]; 550 Leyton Crescent, London, Ontario N6G 1T3 (CA). ZHU, Xizhen [CA/CA]; Apartment 13, 534 Platt's Lane, London, Ontario N6G 3A8 (CA). (74) Agent: DEETH WILLIAMS WALL; National Bank Building, Suite 400, 150 York Street, Toronto, Ontario M5H 3S5 (CA).		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: PREPARATION OF RADIOLABELLED HALOAROMATICS VIA POLYMER-BOUND INTERMEDIATES (57) Abstract According to a first aspect of the invention, a process is disclosed for the preparation of radiolabelled haloaromatic compounds. According to a second aspect of the invention, intermediate precursor insoluble polymer compounds used in the preparation of the radiolabelled haloaromatics are disclosed, as well as processes for the preparation of the intermediate precursor insoluble polymer compounds.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PREPARATION OF RADIOLABELLED HALOAROMATICS VIA POLYMER-BOUND INTERMEDIATES

5 **TECHNICAL FIELD**

This invention relates to the preparation of a radiopharmaceutical. In particular, this invention relates to a process for the preparation a radiolabelled haloaromatic, as well as intermediate precursor compounds used in the process.

10 **BACKGROUND ART**

A number of radiolabelled haloaromatic compounds have found application in nuclear medicine. For example, *meta*-iodobenzylguanidine ("MIBG"), when radiolabelled with the iodine atom, is used in nuclear medicine as either an imaging agent for diagnosis, or as a therapeutic agent for neural crest tumors such as neuroblastoma. When labelled
15 with the shorter-lived iodine-123, [¹²³I]MIBG provides diagnostic cardiac images as well as images of tumors. The longer-lived [¹³¹I]MIBG is used at much higher radiation and chemical doses for the treatment of tumors.

By far the most common method of producing either [¹²³I]MIBG or [¹³¹I]MIBG is by a Cu⁺ catalyzed isotopic exchange process which commences with 1-2 mg of MIBG
20 and the desired amount of radioiodide. Because isotopic exchange is an equilibrium process, the product obtained by this process necessarily contains a significant amount of carrier MIBG. Considerable effort¹ has been placed towards developing a convenient procedure that proceeds in near quantitative radiochemical yields. However, this method has the drawback of producing [¹³¹I]MIBG of low specific activity resulting in chemical doses
25 of 1-5 mg when therapeutic samples are prepared. Doses of this magnitude carry potential hypertensive side effects.

Accordingly, routes to no-carrier-added [^{131}I]MIBG have been developed which could reduce the chemical dose of MIBG by about a factor of 100. Precursors to no-carrier-added [^{131}I]MIBG, such as 3-tributylstannylbenzylamine², 3-trimethylsilylbenzylguanidine², and 3-trimethylstannylguanidinium³, have not found
5 widespread application. These compounds have a short shelf life, and must be stored in a freezer shielded from light.

United States Patent No. 5,565,185 discloses a no-carrier-added process of radiolabelling MIBG by halodestannylation. However, the process is disadvantageous in that a number of impurities remain in solution with the radiolabelled MIBG. In particular,
10 toxic tin by-products remain in solution and must be separated before the radiolabelled MIBG is ready for use.

Accordingly, there is a need for a process for no-carrier-added synthesis of radiolabelled haloaromatic compounds, which can be easily and practically separated from possibly toxic impurities.

15

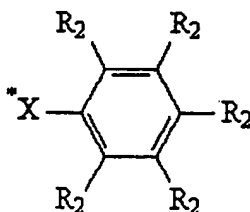
DISCLOSURE OF INVENTION

It is an object of the invention to provide a process for no-carrier-added synthesis of radiolabelled haloaromatic compounds, where the impurities can be removed by simple filtration, thereby making the process suitable for "kit" formulation.

20

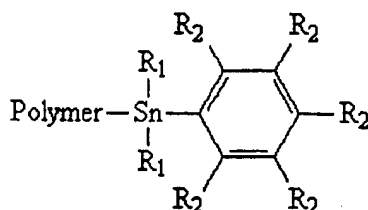
It is also an object of the invention to provide intermediate insoluble polymer precursors which have a long shelf life and can be stored at room temperature without special conditions, and to which the unlabelled compounds and side products are bound, thereby facilitating removal of these undesirable impurities by filtration.

According to a first aspect of the present invention, a process of preparing a radiolabelled haloaromatic compound (I) of the formula:



is provided, wherein,

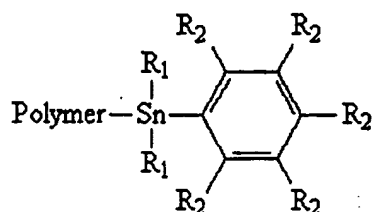
R₂ is selected from an alkyl group, an aryl group, a hydrogen atom, a halogen atom, a substituted oxygen atom, a substituted nitrogen atom, a substituted sulfur atom, a carbonyl group, a cyano group, an amino group, and a guanidino group. *X is selected from any suitable radiohalide, and is preferably selected from ¹²³I, ¹²⁵I, and ¹³¹I. The process comprises reacting an insoluble polymer compound (II) with a radiohalogen ion in the presence of an oxidant and a preferably organic solvent, where compound (II) has the formula:



wherein,

R₁ is an alkyl group, and is preferably a butyl group. R₂ is as described above.

According to a second aspect of the invention, an intermediate insoluble polymer compound is provided. The compound comprises the repeating unit formula:

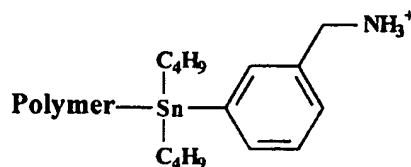


wherein,

R₁ is selected from an alkyl group; and

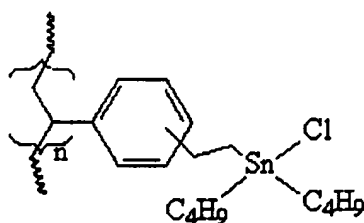
- 5 R₂ is selected from an alkyl group, an aryl group, a hydrogen atom, a halogen atom, a substituted oxygen atom, a substituted nitrogen atom, a substituted sulfur atom, a carbonyl group, a cyano group, an amino group, and a guanidino group.

According to a third aspect of the invention, a process of preparing an intermediate insoluble polymer compound of formula:

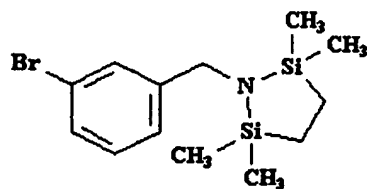


10

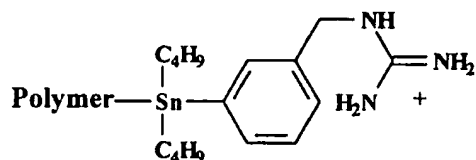
is provided. The process comprises reacting the compound of formula:



with a 1-(3-bromobenzyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine compound of the structural formula:

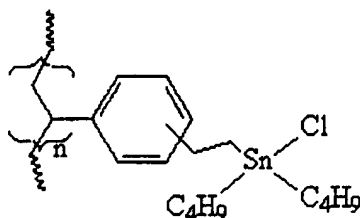


According to a fourth aspect of the invention, a process is provided for preparing an intermediate insoluble polymer compound of formula:

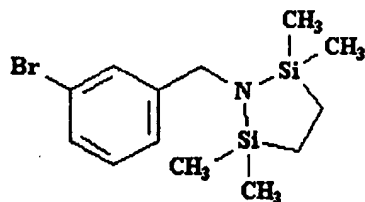


5 comprising the steps of:

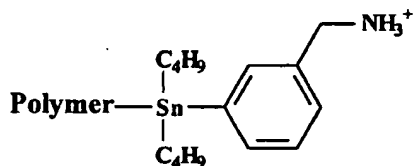
(a) reacting a first insoluble polymer compound of formula:



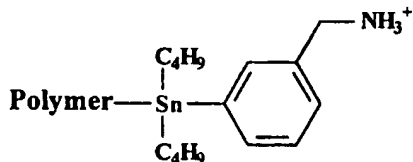
with a 1-(3-bromobenzyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine compound of the structural formula:



to produce the compound having the formula:



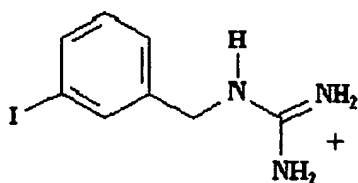
(b) reacting a compound having the formula:



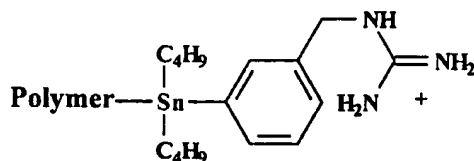
with toluene and NCNH_2 to convert the ammonium group to a guanidinium group.

According to a fifth aspect of the invention, a process is provided for

5 preparing a compound of the formula:



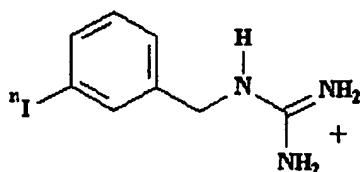
comprising contacting a compound of the formula:



with iodine in an organic solvent.

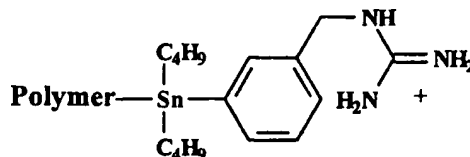
According to a sixth aspect of the invention, a process is provided for

preparing a compound of the formula:



wherein n is selected from 123, 125, and 131;

the process comprising contacting a compound having the formula:



with a solution of Na¹²⁵I and an oxidizing agent in the presence of a buffering agent; wherein n is as described above.

5 Further features of the invention will be described or will become apparent in the course of the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

In order that the invention may be more clearly understood, the preferred
10 embodiment thereof will now be described in detail by way of example, with reference to the accompanying drawings, in which:

Fig. 1A shows the ¹¹⁹Sn MAS NMR spectrum for Polymer 1;

Fig. 1B shows the ¹¹⁹Sn MAS NMR spectrum for Polymer 1 after hydrolysis;

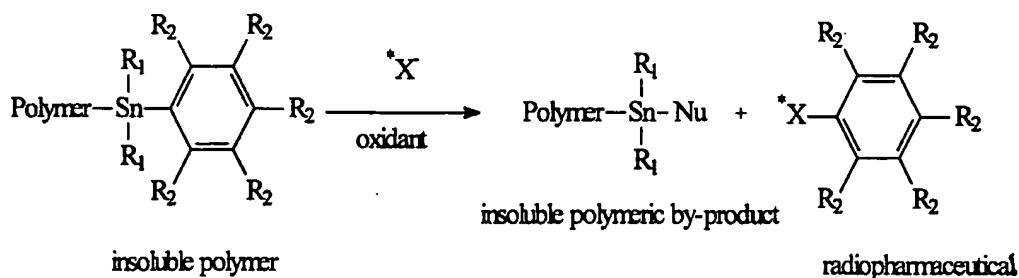
Fig. 1C shows the ¹¹⁹Sn MAS NMR spectrum for Polymer 2;

15 Fig. 1D shows the ¹¹⁹Sn MAS NMR spectra for Polymer 3 recovered after iodination; and

Fig. 2 shows the HPLC analysis of the iodination products of reaction of Polymer 2 with cyanamide at selected reaction times.

BEST MODE FOR CARRYING OUT THE INVENTION

20 The process, according to the present invention, provides for the radiohalogenation of a haloaromatic compound using a polymer-supported pharmaceutical, as follows:



wherein:

R₁ is an alkyl group, and is preferably a butyl group.;

R₂ is selected from an alkyl group, an aryl group, a hydrogen atom, a halogen atom, a substituted oxygen atom, a substituted nitrogen atom, a substituted sulfur atom, a carbonyl group, a cyano group, an amino group, a guanidino group;

Nu is a nucleophile provided by the solvent or oxidant; and

*X is selected from any suitable radiohalide, such as, for example, ^{131}I or ^{123}I .

Although the preferred embodiment of the present invention refers to isotopes of Iodine only, such references are intended by way of example, and are not intended to be limiting. The present invention may be applied to any suitable radiohalide.

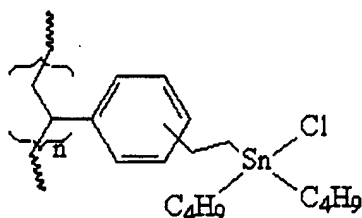
According to a preferred embodiment of the present invention, a process is provided to synthesize no-carrier-added [¹³¹I]MIBG or [¹²³I]MIBG using polymer-supported radiopharmaceutical precursors⁴. An insoluble polymer is prepared in which the pharmaceutical to be radiohalogenated is bound to the polymer through a tin-aryl bond as illustrated above. Treatment with the radiohalide and an appropriate oxidant results in the release of the radiohalogenated pharmaceutical while unreacted polymer and polymer side-products remain insoluble and easily removed by filtration.

The polymer above is derived by reaction of the appropriate organolithium
20 with a polymeric chlorostannane. Polymer 1, described in detail below, is used as an

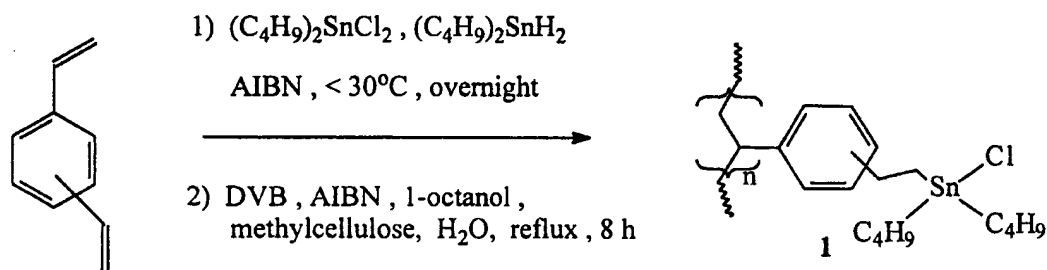
intermediate compound to derive the polymers to be used in the radiohalogenation of a haloaromatic compound. Polymer 2 is one such reagent derived from Polymer 1, and Polymer 3 is the preferred polymer-supported 3-benzylguanidinium reagent for the preparation of no-carrier-added [^{131}I]MIBG or [^{123}I]MIBG. Polymers 2 and 3 are also described in detail below.

Preparation of Poly-3-and -4-(2-dibutylchlorostannyl ethyl)styrene: Polymer 1

Polymer 1 has the following structural formula:



and was prepared by a known procedure⁵, as shown schematically below.



After being run through a short silica column to remove antioxidant, commercial divinylbenzene (36 g, 225 mmol) and di-n-butylchlorostannane (35 g, 115 mmol) were reacted overnight under nitrogen with dibutylstannane (27.5 g, 115 mmol) in the presence of AIBN (0.75 g, 4.6 mmol) near or below 30°C. Then divinylbenzene (6.5 g, 40.6 mmol), AIBN (1.25g, 7.6 mmol), 1-octanol (85.5g) and methyl-cellulose (0.63 g) dissolved in water (250 mL) were added to the previously prepared monomer. This mixture was refluxed for 8 h in a resin kettle under nitrogen with rapid stirring (1000 rpm).

After cooling, water was added to the resin kettle and the solution was decanted from the granular polymer particles. Washing with water was continued until the supernatant ran clear. After a similar treatment with acetone (5 x 200 mL), the polymer was filtered with a coarse sintered-glass funnel and washed with methanol (2 x 200 mL), toluene
5 (3 x 200 mL) and THF (3 x 200 mL). After drying overnight under vacuum at room temperature, 66.5g (73% yield by weight) of white grainy solid was obtained.

The characteristics of Polymer 1 are preferably as follows:

- Solid-state MAS ^{13}C NMR (swollen with CHCl_3), δ ppm: 14.6 (CH_3), 18.6 (Sn-CH_2 -), 27.7 ($-\text{CH}_2\text{CH}_2\text{CH}_3$), 28.6 ($-\text{CH}_2\text{CH}_3$), 42 (broad, Ar-CH- , Ar-CH_2 - and backbone $-\text{CH}_2$ -), 128
10 (broad, aryl CH), 144 (broad, Aryl C).
- Solid-state MAS ^{119}Sn NMR (swollen with CHCl_3), δ ppm.: 148.
- DRIFT spectrum, cm^{-1} : 3036, 3060 (aromatic C-H); 2968, 2938, 2879, 2860 (aliphatic C-H); 1604, 1510 (aromatic C=C vibrations), 1486, 1450. 2968, 2938, 2879, 2860 (aliphatic C-H); 1604, 1510 (aromatic C=C vibrations), 1486, 1450.

15

Samples of Polymer 1 were prepared as indicated above. Polymer 1 was characterized both chemically and spectroscopically. The availability of Sn-Cl bonds was assessed by treatment of Polymer 1 with KOH in ethanol/THF at room temperature. Polymer 1 (201 mg) was soaked in 7 mL of absolute ethanol, 3 mL (3 mmol) of 1 M potassium hydroxide, and 1 mL of tetrahydrofuran for 24 h at room temperature. The
20 polymer was filtered and washed with 70 % ethanol (5 x 5 mL). The ethanol and THF in the filtrate were removed on rotary evaporator and the residual liquid was transferred into a 50 mL volumetric flask and topped up to the mark with water. Then 20 mL of this solution was diluted to 50 mL Erlenmeyer by addition of 1 M nitric acid. This solution was then titrated for
25 Cl^- following the Mohr procedure.⁶

The amount of chloride ion released was found to be 1.7 ± 0.1 mmol/g of polymer. If the polymer was composed exclusively of the units indicated in the structure shown for Polymer 1, the maximum amount of chloride released would be 2.5 mmol/g of polymer. However, significant amounts of divinylbenzene had been used when forming the polymer and the yield of material was 32 % .

Polymer 1 was also investigated by MAS NMR spectroscopy on samples that had been preswollen with chloroform which had the effect of sharpening the signals. The ^{13}C NMR spectrum was consistent with the anticipated structure showing signals for all of the carbons. The signals for the backbone CH and CH_2 and phenyl carbons were quite broad and indistinct. However, the $\text{CH}_2\text{-CH}_2$ carbons and the carbons on the butyl chains were readily assigned by analogy with non-polymeric species. The ^{119}Sn NMR spectrum (Figure 1A) showed but one peak at 148 ppm consistent with species of the general structure $\text{R}_3\text{Sn-Cl}$. This confirmed that all of the tin atoms were bonded to chlorine in spite of the apparent discrepancy in the hydrolysis results mentioned above. This was particularly reassuring since IR spectra invariably gave a broad absorption near 3500 cm^{-1} which was consistent with hydrolysis of the Sn-Cl bond to Sn-OH. The ^{119}Sn NMR spectrum of hydrolysed material (Figure 1B) was obtained and showed the complete absence of the peak at 148 ppm with a group of peaks appearing at about 90 ppm which confirmed that Polymer 1 has tin bonded exclusively to chlorine and that all of these bonds are available for hydrolysis.

As illustrated in detail below, Polymer 1 was preferably converted in two steps first into Polymer 2 which bears the 3-benzylammonium moiety and then into Polymer 3 functionalised with a 3-benzylguanidinium species.

Preparation of polymer-supported 3-benzylammonium chloride: Polymer 2**Preparation of 1-(3-bromobenzyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine: Compound 4**

The conversion of Polymer 1 into Polymer 2 was preceded by the preparation of 1-(3-bromobenzyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine. 3-Bromobenzylamine hydrochloride (25.0 g, 112.3mmol) was converted to the free base by neutralization with sodium hydroxide and extraction into methylene chloride. Drying and solvent removal resulted in 20.3 g of a brown liquid which was used as such. To the above 3-bromobenzylamine (20.3 g, 109mmol) , in a round bottom flask equipped with a condenser and under argon atmosphere, was added 150mL of methylene chloride and 30.3mL (217mmol) of triethylamine. To this stirred mixture cooled with an ice-bath was added slowly 109mL (109mmol) of 1 M 1,2-bis(chlorodimethylsilyl)ethane dissolved in methylene chloride. During the addition, considerable precipitate formed. The ice-bath was removed and the mixture was stirred for another 6.5 h at room temperature. The white solid was removed by filtration and washed with methylene chloride (2 x 30mL). The filtrate was evaporated using a rotary evaporator resulting in further precipitate formation. Hexanes (100mL) were added to this mixture. The solid was removed by filtration and washed with hexanes (2 x 20mL). After hexane removal from the filtrate, a yellowish liquid was obtained which was distilled to yield 29.0 g (82% yield) of light yellowish liquid (bp. 93-50C/0.05 mm Hg).

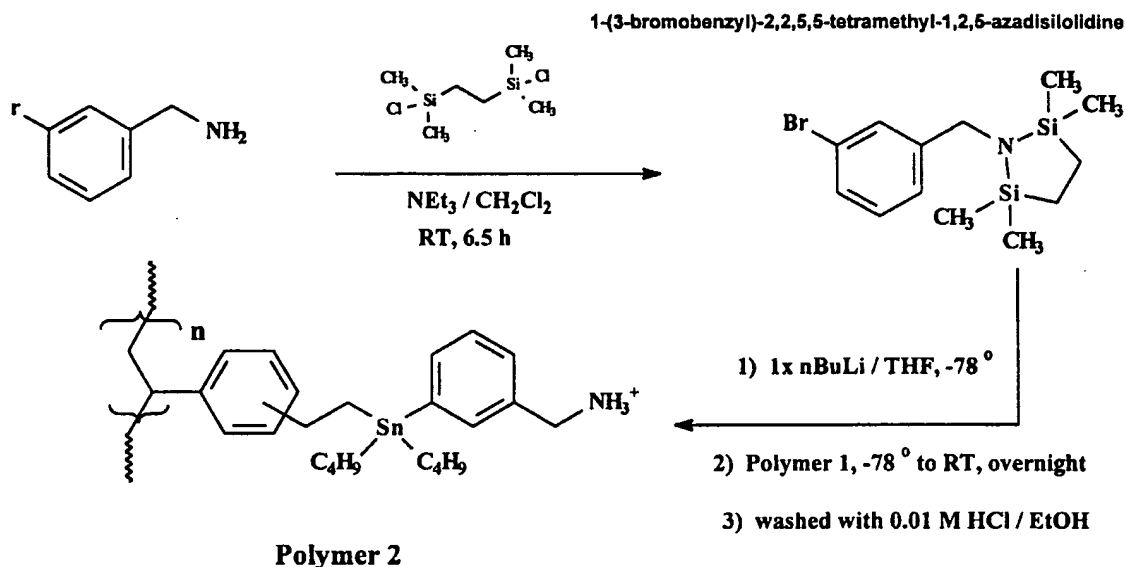
Compound 4 preferably had the following characteristics:

- ¹H NMR spectrum (acetone-d₆): δ 0 (s, 12H, CH₃); 0.79 (s, 4H, Si-CH₂-CH₂-Si); 4.05 (s, 2H, Ar-CH₂-N); 7.25 (t, 1 H, 5-H), 7.30 (d, 1 H, 6-H), 7.38 (d, 1 H, 4-H), 7.47 (s, 1 H, 2-H).
- ¹³C NMR spectrum (chloroform-d): δ 0 (CH₃); 8.2 (Si-CH₂-CH₂-Si); 45.8 (Ar-CH₂-N); 122.4 (C-3), 126.3 (C-6), 129.5 (C-5), 129.7 (C-2), 130.9 (C-4), 146.2 (C-1). IR (neat):

cm⁻¹ 3068 (aromatic C-H stretch); 2949, 2903, 2857 (aliphatic C-H stretch); 1604, 1484 (aromatic C=C vibrations); 849 (vs asymmetric (Si-N-Si stretching), 784(ρ CH₃), 678 (ν_{as} Si-C). (aromatic C-H bending). MS: M/Z 329, 327, 314, 312, 169, 130, 116, 100, 90, 73, 59, 45. Anal. required for C₁₃H₂₂BrNSi₂, m/e 327.0474; found, m/e 327.0479.

5

Following the preparation of 1-(3-bromobenzyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine, the preparation of Polymer 2 proceeded as follows:



10

To 25.0 g (76.1 mmol) of Compound 4 in a three-neck flask equipped with an argon inlet, a serum cap and a powder addition sidearm containing Polymer 1 (28.6 g) was added 250 mL of freshly distilled dried tetrahydrofuran. To this flask cooled to -78°C was added slowly 30.5 mL (76.1 mmol) of 2.5 M n-butyllithium. The initially colourless solution turned purple and then brownish at 25 min. Polymer 1 was then tipped into the reaction solution and the mixture was stirred gently in the dry-ice-acetone bath for 7 h. After the temperature was allowed to rise to room temperature over 2 h and then held at room temperature for another 1h, methanol (10 mL) was added followed by sufficient 1M

15

hydrogen chloride to give a pH of 4-5. The mixture was stirred overnight and allowed to stand unstirred for 15 min.

After the upper cloudy solution was decanted, 200 mL of methanol was added. Again the cloudy upper layer was decanted and this process was repeated 4 times.

- 5 The polymer was filtered through a coarse sintered glass funnel and washed with 50% methanol/water solution (100 mL), methanol (3 x 100 mL), and 95% ethanol (50 mL). After vacuum drying at room temperature, 30.1 g (84 wt % yield) of a white grainy material was obtained.

The characteristics of Polymer 2 were preferably as follows:

- 10 • Solid-state MAS ^{13}C NMR spectrum: δ 14.6 (CH_3), 18.6 (Sn-CH_2), 27.7 ($-\text{CH}_2\text{CH}_2\text{CH}_3$), 28.6 ($-\text{CH}_2\text{CH}_3$), 42 (broad, Ar-CH- , Ar-CH_2- and backbone $-\text{CH}_2-$), 128 (broad, aryl CH), 144 (broad, Aryl C)
- Solid-state MAS ^{119}Sn NMR spectrum: δ -43.6 ppm
- IR spectrum (KBr): cm^{-1} 3435 (broad, $-\text{NH}_3^+$ stretches); 3027 (aromatic C-H stretch);
- 15 2927, 2857 (aliphatic C-H stretches); 1611, 1498 (aromatic C=C vibrations).

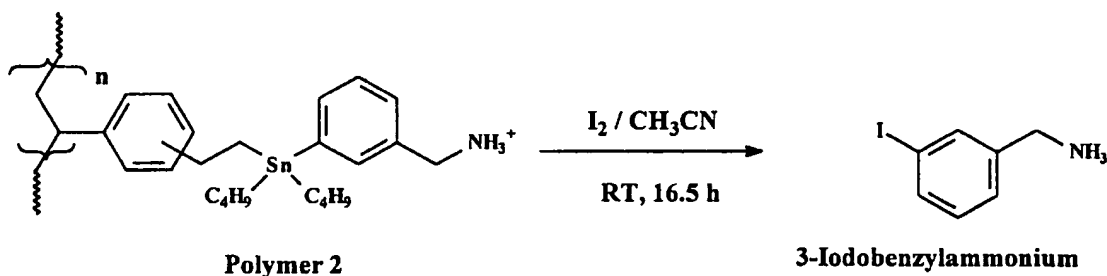
Because 3-bromobenzyl amine has reactive NH bonds, the amino group was first protected as an azadisilolidine⁷ and then reacted with one equivalent of n-butyllithium. Polymer 1 was added to the presumed monolithium species so prepared. Polymer 2 was characterized by ^{13}C and ^{119}Sn MAS NMR spectroscopy.

- 20 The ^{13}C NMR spectrum was consistent with the proposed structure. Again, the signals attributed to the backbone CH and CH_2 carbons and the phenyl carbons appeared as broad peaks. The peaks due to the $\text{Sn-CH}_2\text{-CH}_2$ carbon was identifiable as well as the carbons of the n-butyl group. The benzylic carbons were not readily identified. Perhaps most characteristic was the shift in the $\text{Sn-CH}_2\text{-C}_3\text{H}_7$ carbon signals from 18.6 ppm
- 25 for Polymer 1 to 10.5 ppm for Polymer 2. Again the IR spectrum gave a broad absorption

near 3500 cm^{-1} indicating that considerable hydrolysis accompanied this reaction. However as indicated in Figure 1C, the ^{119}Sn spectrum showed primarily one peak at -43.6 ppm with a small peak at 90ppm consistent with SnOH and representing about 10 % of the tin signals. Thus it would seem that all of the Sn-Cl bonds had reacted with the organolithium reagent
5 with a small amount of concurrent hydrolysis.

Iodination of Polymer 2

The iodination of Polymer 2 proceeded in accordance with the following reaction:



10

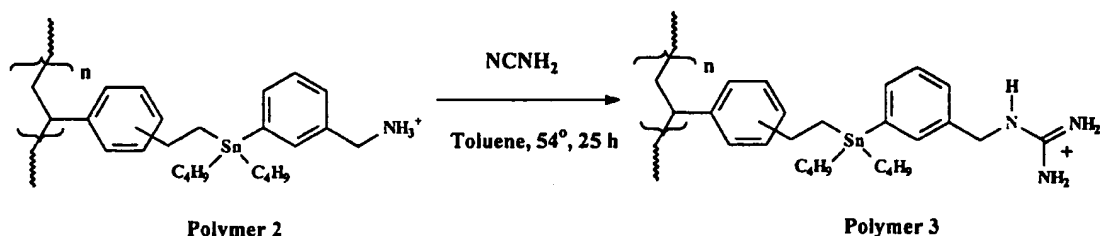
To the previously prepared Polymer 2 (100 mg) was added 10 mL of methanol and 1 mL of 0.2 M iodine in acetonitrile solution. After stirring gently at room temperature for 16.5 h, 1 mL of 1.0 M sodium metabisulphite solution was added. The mixture was transferred into a 100 mL volumetric flask and topped up to 100 mL with 0.01 M
15 KH_2PO_4 . An aliquot was filtered through a syringe filter, and the filtrate was analyzed by HPLC. The retention time of 3-iodobenzylammonium peak was 8.8 min and the amount was determined by comparison to a standard 3-iodobenzylammonium hydrochloride solution (0.4 mM).

The extent of reaction in forming Polymer 2 and the availability of the 3-
20 benzyl ammonium species in Polymer 2 was probed by reaction with iodine as illustrated above. This was anticipated to yield the 3-iodobenzyl ammonium ion ("MIBA") which was

identified and quantified by HPLC. It was found that about 0.95 ± 0.05 mmol/g of 3-iodobenzyl ammonium ion was released per gram of Polymer 2. Again this was somewhat less than the maximum calculated amount if Polymer 2 had the structure indicated above. However, ^{119}Sn NMR spectroscopy proved to be of considerable value as shown in Figure 1D. A comparison of Figure 1C for Polymer 2 and Figure 1D for polymer 2 recovered after iodination shows a complete loss of the signal at -43.6 ppm consistent with complete release of the 3-benzyl ammonium group.

Preparation of polymer-supported 3-benzylguanidinium chloride: Polymer 3

Preferably, the synthesis of Polymer 3 involved treatment of Polymer 2 with a large excess of cyanamide to convert the ammonium group into a guanidinium group, as illustrated below.



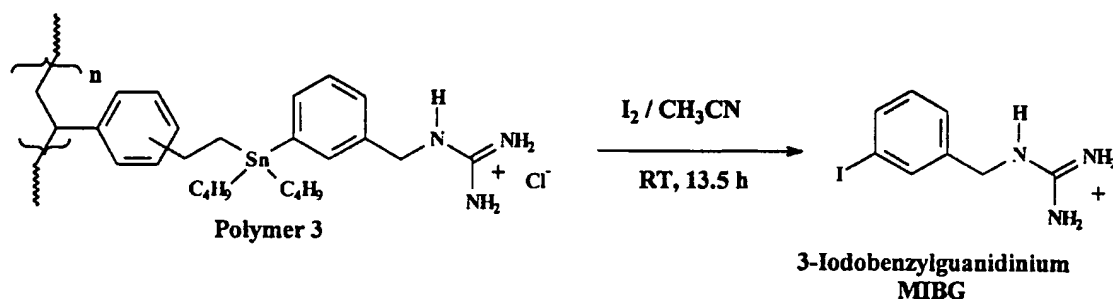
Under an argon atmosphere, 20.0 g of Polymer 2, 15.1 g (360mmol) of cyanamide, 100 μL (0.72mmol) of triethylamine and 250mL of toluene were added to a flask equipped with a reflux condenser. The mixture was heated for 25 h at 54°C and the hot reaction mixture was filtered through a coarse sintered glass funnel. The polymer was washed with acetonitrile (4 x 100 mL), methanol (4 x 100 mL) and acetonitrile (2 x 100 mL). After vacuum drying at room temperature overnight, 20.7 g of white grainy material was obtained.

The characteristics of Polymer 3 are preferably as follows:

- IR spectrum (KBr): cm^{-1} 3340, 3271, 3174 (N-H stretch); 3066, 3027 (aromatic C-H stretch); 2978, 2929, 2880, 2860 (aliphatic C-H stretch); 1677, 1658 (C=N stretch); 1521, 1496 (aromatic C=C vibrations); 719 (aromatic C-H bend).

Iodination of Polymer 3

- 5 The iodination of Polymer 3 proceeded in accordance with the following reaction:



- To 26.4 mg of Polymer 3 suspended in 4 mL of methanol was added 300 μL of 0.2 M iodine in acetonitrile solution. After stirring for 13.5 h at room temperature, 0.1 mL of 1 M sodium metabisulphite solution was added. The mixture was transferred into a 100 mL volumetric flask and topped up to 100 mL with 0.01 M KH_2PO_4 buffer. After filtering through a syringe filter, the filtrate was analysed by HPLC by comparison to standard 3-iodobenzylammonium chloride solutions (0.4 mM) and 3-iodobenzylguanidinium chloride solutions (0.2 mM) which had a retention times of 8.7 min and 15.6 min respectively.

- 15 Unreacted ammonium groups resulted in the release of the 3-iodobenzyl ammonium ion while ammonium groups that had reacted with cyanamide would result in the release of the 3-iodobenzyl guanidinium ion, as illustrated above. Thus, at selected time intervals, polymeric material was isolated from the reaction mixture and treated with an excess of iodine. After reduction of the iodine, aliquots were analyzed by HPLC and the results are presented in Figure 3. At 75 $^{\circ}\text{C}$ after 1h, 80 % of the ammonium groups had
- 20

been converted to guanidinium groups and by 2 h conversion had progressed to 96.2 %. By 5h, there was less than 0.3 % of unreacted ammonium groups.

However, a new peak with a retention time slightly longer than the 3-iodobenzyl guanidinium was observed. This material was identified to be the 3-iodobenzylbiguanidinium ion in two ways. First, an authentic sample of 3-iodobenzylbiguanidinium nitrate was produced⁸, as described in detail below. The sample was found to have an identical retention time with the new peak. Secondly, a small sample of the new material was isolated from a reaction that was allowed to run considerably longer and at a higher temperature than those shown in Figure 2. Although not enough material could be isolated in a sufficiently pure form to allow a mixed mp., the ¹³C NMR spectrum was identical with the authentic sample of 3-iodobenzylbiguanidinium nitrate that had been produced. The guanidinium group reacted further with cyanamide, but at a rate considerably slower than the ammonium group so that the biguanidinium species does not start to appear until very late in the conversion process.

With this time course in mind, a reasonably large batch of polymer 2 was reacted for 25 h. at 54°C. After the usual washing, Polymer 3, so produced, was analyzed by iodination to yield 3-iodobenzyl guanidinium at a level of 1.1 ± 0.05 mmol/g of Polymer 3.

Preparation of 3-iodobenzylbiguanidinium nitrate

In a 25 mL flask, 3-iodobenzylamine hydrochloride (2.0 g, 7.4 mmol) was combined with 0.62 g (7.4 mmol) of dicyandiamide and an argon atmosphere was introduced. The mixture was melted at 154°C for 30 min and water (20 mL) was added to dissolve the brownish solid. HPLC analysis showed 8 mol % of 3-iodobenzylamine hydrochloride, 17 mol % of MIBG and 75 mol % of 3-iodobenzylbiguanidinium nitrate (excluding dicyandiamide at 9.6 min) with a retention times of 6.1 min, 11.2 min and 12.7

min respectively. After decolorizing with charcoal, the solution was adjusted to pH~9 with saturated sodium carbonate. The upper aqueous solution was decanted from the oil which was separated. Water (5 mL) was added to the oil followed by 1 M nitric acid to a pH~5. A lot of bubbles formed during the addition of nitric acid and the mixture turned into a clear solution at pH~5. White crystals formed about 1 minute later.

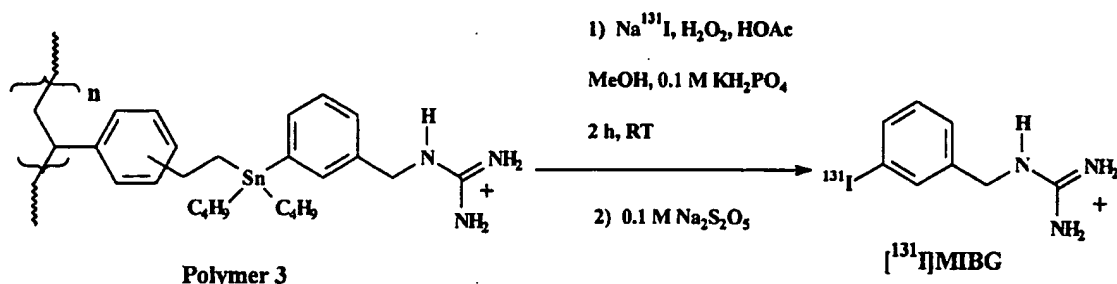
After 20 min. at room temperature, the crystals were collected by filtration and washed with water (3 x 3 mL). After drying, 1.22 g of white crystals were obtained. Concentration of the filtrates to about 10 mL yielded 0.23 g more of white crystals. The two batches of crystals were combined and recrystallized using acetonitrile (25 mL) to provide 0.25g of white mushroom shape crystals. HPLC analysis showed 99 mol % of 3-iodobenzylbiguanidinium nitrate, 1 mol % of MIBG and dicyandiamide. The 0.25 g of crystals were recrystallized again from 6 mL of acetonitrile to yield 99.3 mg (4 % yield) of white mushroom shape crystals of mp 133.5-134.5°C.

The characteristics of the 3-iodobenzylbiguanidinium nitrate were preferably as follows:

- ^1H NMR spectrum (methanol- d_4): δ 4.34 (d, 2H, CH_2), 7.05 (t, 1H, 5-H), 7.28 (d, 1H, 6-H), 7.56 (d, 1H, 4-H), 7.63 (s, 1H, 2-H).
- ^{13}C NMR spectrum (methanol- d_4): δ 45.5 (CH_2), 95.3 (C-3), 127.9 (C-6), 131.5 (C-5), 137.4 (C-2), 137.5 (C-4), 142.4 (C-2), 160.3 (middle C=N), 162.1 (terminal C=N).
- FT-IR spectrum (KBr): cm^{-1} 3506, 3467, 3428, 3330, 3301, 3213 (N-H stretch); 2968.1, 2938.9 (aliphatic C-H stretch); 2440 ($-\text{NH}_2^+$ stretch); 1658, 1638 (C=N stretch); 1555 (asymmetric NO_3^- stretch); 1428.0, 1394 (symmetric NO_3^- stretches); 782 (aromatic C-H bend).
- UV spectrum: $\delta_{\text{max}}=232\text{nm}$, $\epsilon_{\text{max}}=2.49 \times 10^4$. Anal. calc'd for $\text{C}_9\text{H}_{13}\text{IN}_6\text{O}_3$: C, 28.44; H, 3.45; N, 22.11; I, 33.38. Found: C, 28.61; H, 3.44; N, 22.07; I, 33.19.

Radioiodination of Polymer 3

Following the successful completion of the iodination of Polymer 3, the radioiodination of Polymer 3 using sodium [^{131}I]iodide, proceeded in accordance with the following reaction:



5

Into a 2 mL vial was placed 0.5 mg of Polymer 3, 300 μL of methanol, 100 μL of 0.1 M potassium dihydrogen orthophosphate, 45.5 MBq of a Na^{131}I solution and a 100 μL aliquot of a solution prepared from 2 mL of acetic acid and 2 mL of 50 % hydrogen peroxide solution diluted to 50 mL with water. The mixture was occasionally shaken for 2 h at room temperature and then 200 μL of 0.1 M sodium metabisulphite was added to the reaction mixture.

After filtration through a syringe filter, the filtrate was analyzed by HPLC. The UV detector trace showed a large peak at the solvent front and several smaller peaks well before MIBG peak. The corresponding radioactivity detector trace showed two peaks at 1.9 and 15.6 min which were confirmed by coinjection to be $^{131}\text{I}^-$ (2.4 %) and [^{131}I]MIBG (97.6%) respectively.

An aliquot of the reaction mixture, 25.4 MBq, was passed through a Sep-PakTM cartridge and washed with 5 mL of water. Radioactivity was found in the washes, 1.0 MBq, and on the cartridge, 24.4 MBq. Washing of the cartridge with 1.3 mL of 42% ethanol, released 20.0 MBq of radioactivity into the washes. A wash with 1 mL of methanol released

20

a further 3.1 MBq of [^{131}I]MIBG for a total of 23.1 MBq (95 %). The washes were analyzed by HPLC. The trace from the UV detector showed two small peaks at the solvent front and a peak at 15.6 min which, by coinjection, was confirmed to be MIBG. The corresponding radioactivity trace showed a single peak at 15.6 min.

5 The success of the radioiodination was assessed by HPLC using both an UV detector and a γ -ray detector. The oxidant, $\text{H}_2\text{O}_2/\text{HOAc}$, or its by-products are readily separable from any [^{131}I]MIBG produced, and results of this oxidizing system are presented in Table 1. Labelling reactions were run at room temperature on about one or two grains of Polymer 3 in a mixture of methanol and 0.1 M KH_2PO_4 using $\text{Na } ^{131}\text{I}$. Under these conditions
10 after filtration, essentially all of the radioactivity was found in solution either as $^{131}\text{I}^-$ or as [^{131}I]MIBG as evidenced by their HPLC retention times using a radioactivity detector. Table 1 shows the effect on the radiochemical yield of [^{131}I]MIBG of increasing the concentration of H_2O_2 and acetic acid at various reaction times. As the first column indicates, the exclusion of acetic acid from the reaction mixture led to low yields and apparently slow reactions. The
15 third column indicates a general increase in yield with reaction time. At two hour reaction times, increasing concentrations of H_2O_2 and acetic acid led to increased yields which approached near quantitative conversion. It was these conditions that were chosen for preparation of [^{131}I]MIBG, as illustrated.

20 **Table 1.** Radiochemical yield of [^{131}I]MIBG from treatment of Polymer 3 with $\text{Na } ^{131}\text{I}$ and $\text{H}_2\text{O}_2/\text{HOAc}$ as oxidant as a function of reaction time and oxidant concentration

Reaction ^a time (min)	[H_2O_2], mM / [HOAc], mM				
	50 / 0	20 / 24	37 / 42	50 / 57	60 / 68
30	0		30		
60		30	70	63	
120		45	80	90	98
150	56				
180			85		

^a Reactions were run at room temperature in a mixture of methanol and 0.1M KH_2PO_4 .

Purification of the product from the radiolabelling reaction involved two steps. The first was simple filtration through a syringe tip filter. An HPLC analysis of this product using a UV detector showed a large peak at the solvent front and several minor peaks. The radioactivity detector showed two peaks corresponding to ^{131}I - at about 2 % and the other to ^{131}I]MIBG at 98 %. The second step in the purification involved selective absorption and desorption of the ^{131}I]MIBG onto a C18 Sep-Pak™ cartridge. When the primarily aqueous solution from the filtration step was passed through the C18 Sep-Pak™ cartridge, essentially all of the radioactivity was absorbed onto the cartridge with the small amount of iodide passing through. When the cartridge was washed with ethanol/water, 82 % of the radioactivity was released. A further 10 % was released when methanol was used as eluant.

An HPLC analysis of these solutions, using an UV detector, showed two small peaks near the solvent front and a small peak at the retention time of MIBG. The area of this peak was rather too small to allow a reliable calculation of the specific activity of the ^{131}I]MIBG. The corresponding radioactivity trace showed but one peak at the retention time of MIBG. Thus following this procedure, the no-carrier-added ^{131}I]MIBG was produced in about 92 % radiochemical yield with a specific activity of ≥ 500 Ci/mmol..

^{123}I]MIBG was produced using Iodobeads™ as the oxidant, which resulted in a radiochemical yield of about 55 %. Since later experiments with Na^{131}I showed that about 45 % of the radioactivity remained absorbed to the insoluble polymeric materials, this experiment demonstrates that Polymer 3 is an effective precursor to ^{123}I]MIBG. Similar results can also be expected with ^{125}I]MIBG.

The process, according to the present invention, produces no-carrier-added ^{131}I]MIBG in ≥ 90 % radiochemical yield and high chemical purity. Isolation and purification are simple, involving just filtration and absorption and desorption onto a C18 Sep-Pak™

cartridge. No-carrier-added material should avoid the potential pharmacological side effects accompanying the current method of production.

Although the above description refers to radioiodination of MIBG, such references are not intended to be limiting. The process and intermediate compound
5 according to the present invention can be used for synthesis of any number radiolabelled haloaromatic compounds.

It will be appreciated that the above description relates to the preferred embodiment by way of example only. Many variations on the invention will be obvious to those knowledgeable in the field, and such obvious variations are within the scope of the
10 invention as described and claimed, whether or not expressly described.

INDUSTRIAL APPLICABILITY

The process and precursor compounds, according to the present invention, is useful in the field of nuclear medicine for the production of radiopharmaceutical compounds.

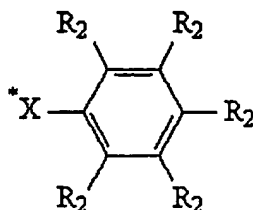
15

References

- 1) Wafelman, A.R., Konings, M.C.P., Hoefnagel, C.A., Maes, R.A.A. and Beijnen, J.H.,
Appl Radiat. Isot., 997 (1994) and references therein.
- 2) Vaidyanathan, G. and Zalutsky, M.R., *Appl Radiat. Isot.*, 621 (1993).
- 5 3) Flanagan, R.J., Goel, A., Charleson, F.P. and Hunter, D.H., *J. Label. Comp. Radiopharm.*, 636 (1995).
Hunter, D.H., Goel, A. and Flanagan, R.J., "Process for the Preparation of Radiolabelled meta-Halobenzylguanidine", *USA Patent No. 5,585,185*.
- 10 4) Culbert, P.A., and Hunter, D.H., Polymer Supported Radiopharmaceuticals: ^{123}I and ^{131}I -
Laabelled N-Isopropyl-4-Iodoamphetamine, *Reactive Polymers*, **19**, 247-253 (1993).
- 5) Gerigk, U., Gerlach, M., Neumann, W.P., Veiler, R. and Weintritt, V., *Synthesis*, 448
(1990).
- 6) R.A. Day, Jr.; A.L. Underwood, *Quantitative Analysis Laboratory Manual* (Prentice-Hall, Inc.), 2nd ed., p. 115-116, Englewood Cliffs, New Jersey, 1967.
- 15 7) Djuric, S., Venit, J., and Magnus, P., *Tetrahedron Lett.*, **22**, 1787-1790 (1981).
- 8) Shapiro, S.L., Parino, V.A., Rogow, E., Freedman, L., *J. Am. Chem. Soc.*, **81**, 3728
(1959).

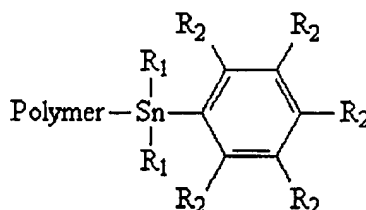
CLAIMS:

1. A process of preparing a radiolabelled haloaromatic compound (I) of the formula:



wherein,

- 5 R₂ is selected from an alkyl group, an aryl group, a hydrogen atom, a halogen atom, a substituted oxygen atom, a substituted nitrogen atom, a substituted sulfur atom, a carbonyl group, a cyano group, an amino group, and a guanidino group;
- *X is selected from any suitable radiohalide;
- said process comprising reacting a radiohalogen ion with a insoluble polymer compound (II)
- 10 in the presence of a solvent and an oxidant, said polymer compound (II) having the formula:



wherein,

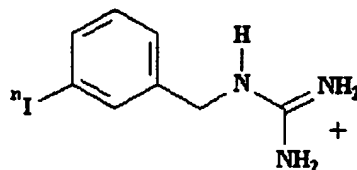
R₁ is an alkyl group; and

R₂ is as described above.

2. The process of claim 1, wherein R₁ is a butyl group.
- 15 3. The process of claim 1, wherein *X is selected from ¹³¹I, ¹²⁵I, and ¹²³I.

4. The process of claim 1, wherein the solvent is an organic solvent.

5. The process of claim 4 where compound (I) has the formula:



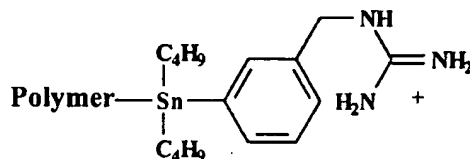
wherein n is selected from 123, 125, and 131.

6. The process of claim 5, wherein n is 123.

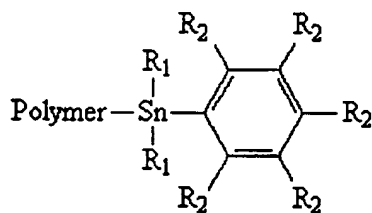
5 7. The process of claim 5, wherein n is 131.

8. The process of claim 5, wherein n is 125

9. The process of claim 5 wherein the polymer compound (II) has the formula:



10. An intermediate insoluble polymer compound of the repeating unit formula:



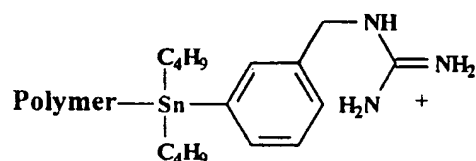
wherein,

10 R₁ is an alkyl group; and

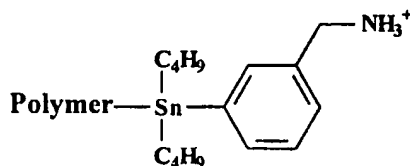
R_2 is selected from an alkyl group, an aryl group, a hydrogen atom, a halogen atom, a substituted oxygen atom, a substituted nitrogen atom, a substituted sulfur atom, a carbonyl group, a cyano group, an amino group, and a guanidino group.

11. The intermediate insoluble polymer compound of claim 10, wherein R_1 is a butyl group.

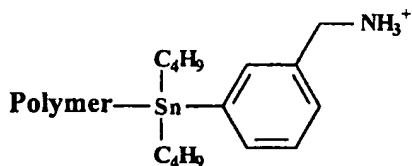
12. The intermediate insoluble polymer compound of claim 11, having the formula:



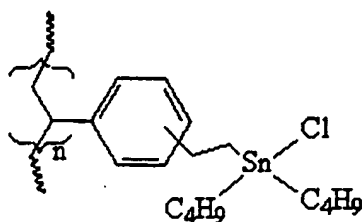
13. The intermediate insoluble polymer compound of claim 11, having the formula:



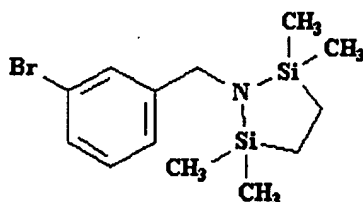
14. A process of preparing an intermediate insoluble polymer compound of formula:



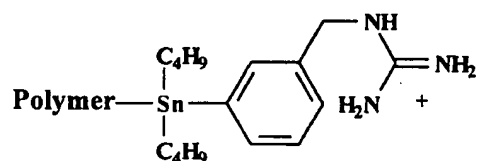
comprising reacting a compound of the formula:



with a 1-(3-bromobenzyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine compound of the structural formula:

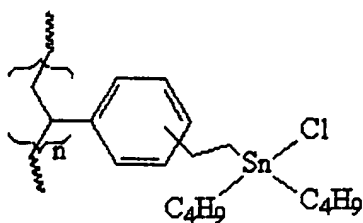


15. A process for preparing an intermediate insoluble polymer compound of the
5 formula:

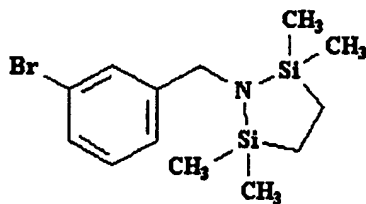


comprising the steps of:

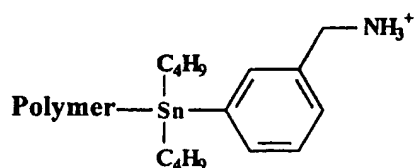
- (a) reacting a first insoluble polymer compound of the formula:



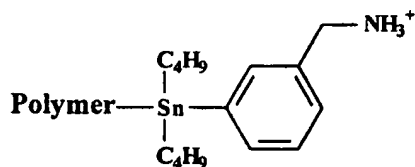
with a 1-(3-bromobenzyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine compound of the structural formula:



to produce the compound having the formula:

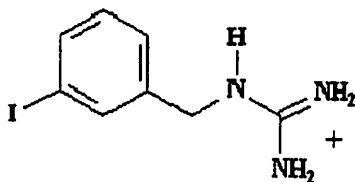


(b) reacting a compound having the formula:

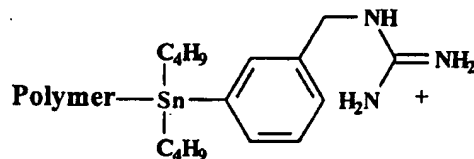


5 with toluene and NCNH_2 to convert the ammonium group to a guanidinium group.

16. A process of preparing a compound of the formula:



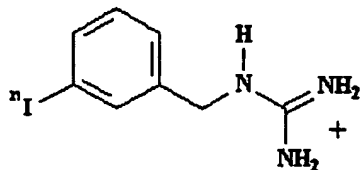
comprising contacting a compound of the formula:



with iodine in an organic solvent.

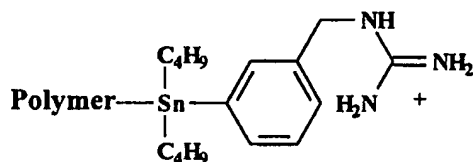
17. The process of claim 16, wherein the organic solvent is selected from one or more of the group comprising acetonitrile and chloroform.

18. A process of preparing a compound of the formula:



5 wherein n is selected from 123, 125, and 131;

said process comprising contacting a compound having the formula:



with a solution of NaⁿI and an oxidizing agent in the presence of a buffering agent;

wherein n is as described above.

19. The process of claim 18, wherein the oxidizing agent is selected from one or
10 more of hydrogen peroxide and acetic acid.

20. The process of claim 18, wherein the buffering agent is KH₂PO₄.

21. The process of claim 18-20, wherein n is 131.

22. The process of claim 18-20, wherein n is 123.

23. The process of claim 18-20, wherein n is 125.

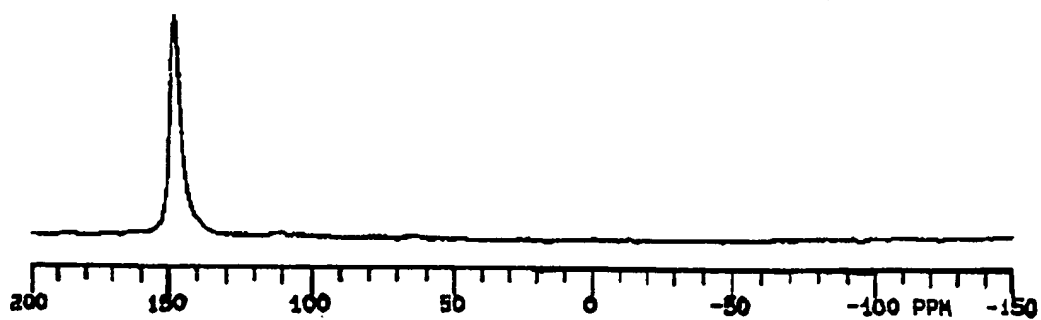


Figure 1A

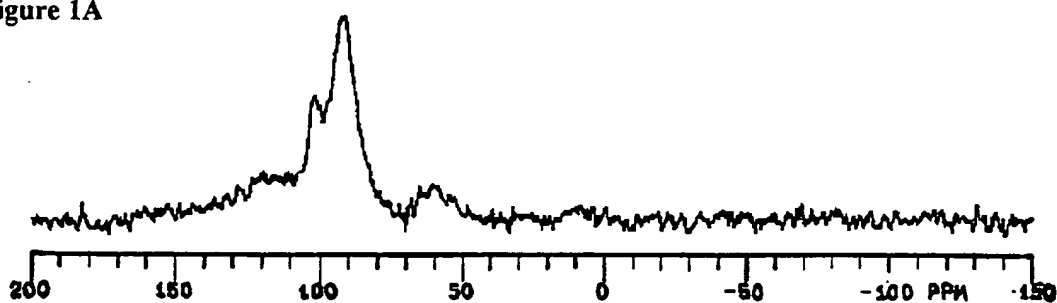


Figure 1B

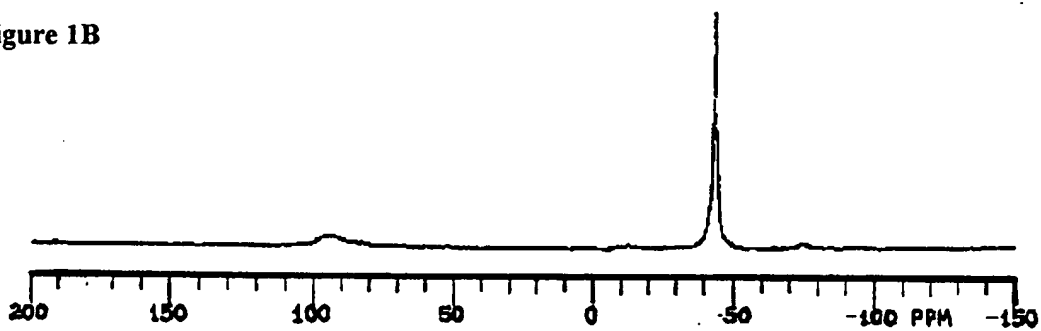


Figure 1C

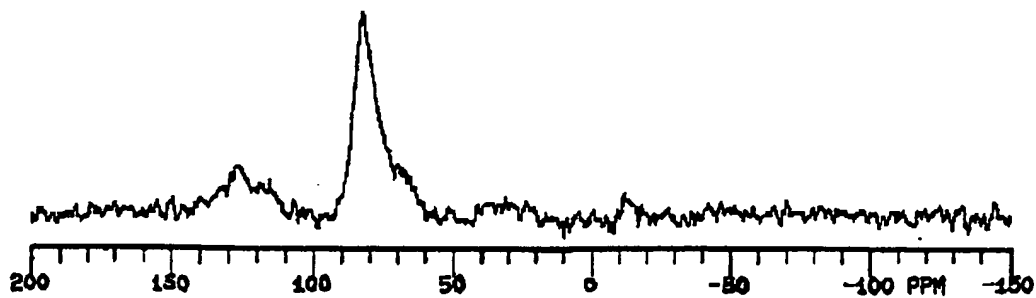
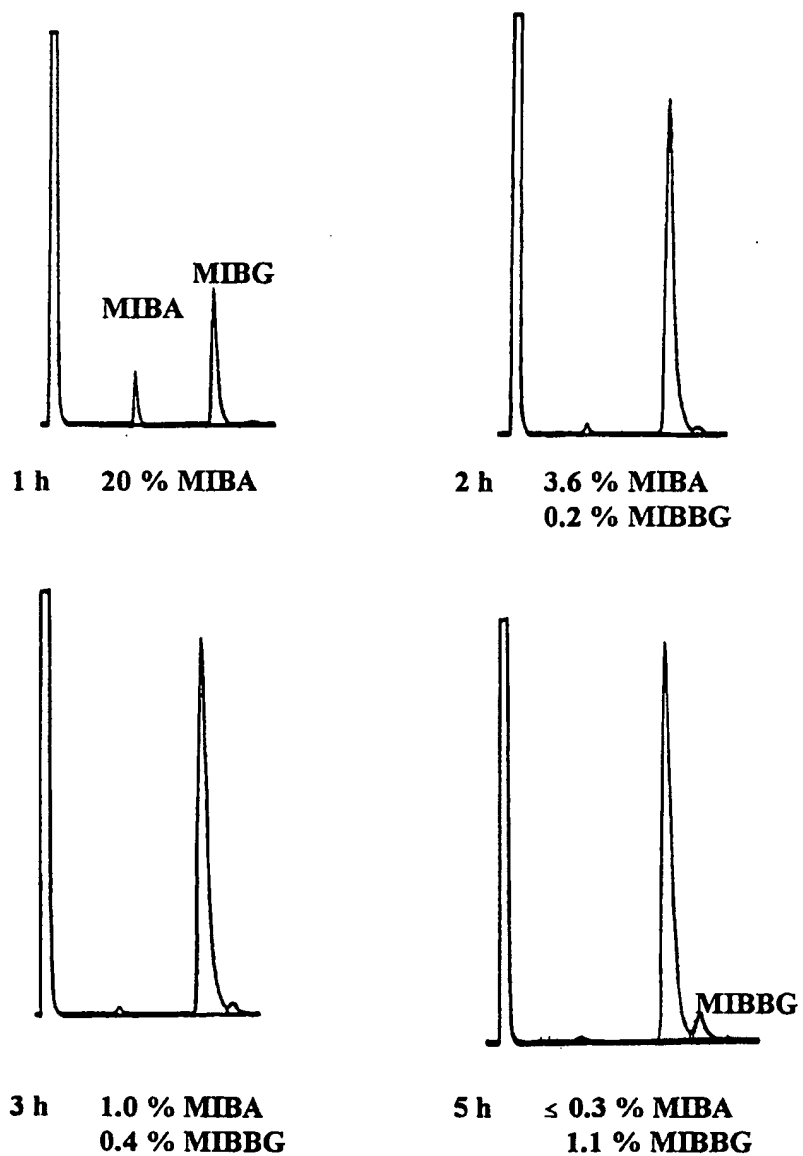


Figure 1D

Figure 2



INTERNATIONAL SEARCH REPORT

National Application No.

PCT/CA 98/00933

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07B59/00 C08F30/04 C07C277/08 C07C279/06 //C07M5:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07B C08F C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P. A. CULBERT: "Polymer-supported radiopharmaceuticals: 123-I- and 131-I-labelled N-isopropyl-4-iodoamphetamine" REACTIVE POLYMERS, vol. 19, 1993, pages 247-253, XP002088253 cited in the application see Fig. 1 and the paragraph bridging pages 250 and 251	1-4, 10, 11
A	EP 0 693 467 A (MERCK FROSST CANADA) 24 January 1996 see claims; examples --- -/--	1-9, 16-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

16 December 1998

Date of mailing of the international search report

14/01/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Wright, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00933

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	G. VAIDYANATHAN: "No-carrier-added synthesis of meta-' ¹³¹ Iodobenzylguanidine" APPLIED RADIATION AND ISOTOPES., vol. 44, no. 3, 1993, pages 621-628, XP002088254 EXETER GB cited in the application see page 624 - page 625 ----	1-9, 16-23
A	A. R. WAFELMAN: "Synthesis, radiolabelling and stability of radioiodinated m-iodobenzylguanidine, a review" APPLIED RADIATION AND ISOTOPES., vol. 45, no. 10, 1994, pages 997-1007, XP002088255 EXETER GB cited in the application see table 3 -----	1-9, 16-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 98/00933

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 693467 A	24-01-1996	US 5565185 A	15-10-1996
		AT 172446 T	15-11-1998
		CA 2153851 A	21-01-1996
		DE 69505465 D	26-11-1998
<hr/>			